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## Cancer treatment induced metabolic syndrome

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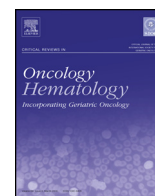
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# Cancer treatment induced metabolic syndrome: Improving outcome with lifestyle



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## ABSTRACT

Increasing numbers of long-term cancer survivors face important treatment related adverse effects. Cancer treatment induced metabolic syndrome (CTIMetS) is an especially prevalent and harmful condition. The aetiology of CTIMetS likely differs from metabolic syndrome in the general population, but effective treatment and prevention methods are probably similar. In this review, we summarize the potential mechanisms leading to the development of CTIMetS after various types of cancer treatment. Furthermore, we propose a safe and accessible method to treat or prevent CTIMetS through lifestyle change. In particular, we suggest that a lifestyle intervention and optimization of energy balance can prevent or mitigate the development of CTIMetS, which may contribute to optimal survivorship care.

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## 1. Introduction

The number of long-term cancer survivors is growing. According to recent data, the age-adjusted 5-year survival in Europe was about 50% for all cancer types (Baili et al., 2015). Factors like bet-

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**Table 1**  
Criteria of the metabolic syndrome according to the NCEP ATP III.

Three or more of the following:		
	Male	Female
Waist circumference (cm)	≥102	≥88
High density lipoprotein cholesterol (HDL-C) (mmol/L)*	<1.03	<1.29
Triglycerides (mmol/L)*	≥1.7	
Blood pressure (mmHg)*	systolic ≥ 130/diastolic ≥ 85	
Fasting plasma glucose (mmol/L)*	≥5.6	

\*Or drug treatment for respectively low HDL, elevated triglycerides, elevated blood pressure or elevated plasma glucose.

ter cancer-care organization (e.g. screening, prevention programs, access to medical facilities), more effective treatment options, evidence based tumour-specific protocols and a more multidisciplinary approach have contributed to this (Baili et al., 2015; Haward, 2006; Haward, 2006). The encouraging increase in overall survival is accompanied by increasing numbers of cancer survivors whose prognosis and quality of life are hampered by the potentially harmful long-term and late side effects of their treatments. Long-term survivors of childhood, breast, colorectal and testicular cancer and of several haematological malignancies face an increased risk of treatment-induced cardiovascular disease (Lenihan and Cardinale, 2012) and metabolic syndrome (MetS) (de Haas et al., 2010). MetS is a clustering of central obesity, insulin resistance, dyslipidaemia and hypertension (de Haas et al., 2010, 2013). This syndrome is associated with inflammatory and prothrombotic features and might be an important link between cancer treatment, cardiovascular toxicity and accelerated atherosclerosis in cancer survivors (Van Gaal et al., 2006). The high prevalence of weight gain and sedentary lifestyle in this population (Irwin, 2009; Kroenke et al., 2005), is a contributing factor to the higher occurrence of MetS and cardiovascular morbidity in cancer survivors. Besides the fact that obesity is rapidly taking over smoking as the most preventable cause of cancer in the United States (Arnold et al., 2015; US Cancer Statistics, 2012), it is plausible that obesity is part of a vicious circle of cancer treatment-related fatigue (Minton et al., 2013), impaired physical function, discomfort, physical inactivity and continued weight gain (Lucia et al., 2003). One of the possible ways to safely and effectively treat MetS in the general population is a lifestyle intervention with the goal to optimize energy balance by increasing physical activity and reducing caloric intake. Although the aetiology of MetS in non-cancer patients probably differs from the aetiology in cancer patients (de Haas et al., 2010), it is reasonable to assume that the same treatment strategies may have similar positive effects on the prevention and treatment of the different components of MetS.

In this review, we focus on the aetiology of the different components of CTIMetS and corresponding measures to prevent or mitigate this syndrome. We summarize different types of cancer and cancer treatments and their relation to CTIMetS. Furthermore, we review if interventions regarding exercise level or diet can influence CTIMetS. Finally, we discuss the influence of timing of these interventions.

## 2. The metabolic syndrome

According to Grundy (2008), at least 25% of the population in the Americas, Europe and India has MetS. The commonly used criteria for MetS are those defined by the National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP) III (Evaluation and Treatment of High Blood Cholesterol in Adult, 2001; Grundy et al., 2005) (Table 1). Patients with MetS are at increased risk of developing a cardiovascular event or type 2 diabetes mellitus (Sattar et al., 2008; Eckel et al., 2010). Early detection of insulin

resistance, dyslipidaemia and/or hypertension or their aetiological factors makes treatment or prevention possible with the aim to reduce cardiovascular morbidity (Eckel et al., 2010). Obesity can be considered as a major driving force in the development of MetS, leading to both cardiometabolic risk and insulin resistance (Giugliano et al., 2008; Kahn, 2007) and is the first component that should be dealt with (Fig. 1). A key aspect of this process is thought to be the release of free fatty acids (FFAs) (Boden, 2008). Adipose tissue stores and releases adipokines and FFAs, which have been linked to insulin-resistance (Boden et al., 1994). More adipose tissue mass releases more FFAs. Moreover, the antilipolytic action of insulin is inhibited by elevated levels of plasma FFAs, which further increases FFA release (Jensen et al., 1989). Obesity and insulin resistance are associated with increased production of very low density lipoprotein triglycerides by the liver. The increase in FFAs and hyperinsulinaemia are believed to be responsible for this (Bamba and Rader, 2007). Insulin resistance reduces endothelial production of nitric oxide, which results in decreased vasodilatation and increased blood pressure, with hypertension occurring more frequently (Boden, 2008).

## 3. Cancer treatment induced metabolic syndrome

The aetiology of CTIMetS is multifactorial and differs between treatment type, cancer diagnosis and patients characteristics. Surgery, radiotherapy, chemotherapy and hormonal therapy have been shown to induce MetS, probably due to different and sometimes overlapping mechanisms (Table 2). In Table 3, an overview of the odds ratios or relative risk of MetS in different patient groups is given.

### 3.1. The role of surgery

Pituitary or hypothalamic damage can result in hormonal disturbances, for example after surgical treatment for brain tumours (Pietila et al., 2009). Pietilä et al. reported that 8% of brain tumour patients, mean age 14.4 years, had MetS, and this was associated with pituitary or hypothalamic damage ( $P=0.003$ ). Additional cranial radiotherapy made these patients even more prone to hormonal disturbances and, as a consequence, to CTIMetS in 20% of the patients (Pietila et al., 2009).

Orchiectomy in testicular cancer survivors may result in gonadal endocrine dysfunction, i.e. low testosterone and/or high luteinizing hormone (LH) levels (primary hypogonadism). After the removal of one testicle, LH may increase, which is probably the result of fewer Leydig cells. The remaining Leydig cells have to be more active to produce sufficient amounts of testosterone. Low testosterone levels are related to CTIMetS (Nuver et al., 2005).

Risk-reducing salpingo-oophorectomy (RRSO) is also strongly associated with CTIMetS. Michelsen et al. (2009) found an association with CTIMetS with an odds ratio (OR) of 2.46 (95% confidence interval (CI) 1.63–3.73) in women who had undergone RRSO (mean follow-up 6.5 years) (Table 3) compared to the general population. Especially waist circumference and central obesity were determinative criteria in the scoring of CTIMetS. Probably, loss of oestrogen causes alterations in body fat distribution with increased waist circumference and central obesity (Michelsen et al., 2009). Careful follow-up for these women is clearly advisable.

### 3.2. The role of radiotherapy

Cranial radiotherapy in particular is strongly associated with disturbances in the hypothalamus-pituitary axis, which has mostly been studied in childhood cancer survivors. For example, deficiency of growth hormone is the most common endocrine dysfunction in patients treated with cranial radiotherapy and is associated with



**Fig. 1.** Physical activity is a safe and effective way of coping with cancer treatment induced metabolic syndrome (CTIMetS) or possibly preventing it. Obesity is frequently the major driving force behind the metabolic syndrome and CTIMetS and is the main target for lifestyle intervention.

**Table 2**

Overview of different types of cancer treatment with possible mechanisms of cancer treatment induced metabolic syndrome (CTIMetS).

Treatment	Specified treatment	Mechanism	Associated with
Surgery	Brain surgery with damage to pituitary and hypothalamus.	Hormonal disturbance: deficiency of growth hormone, thyroidtropin, gonadotropin, adrenocorticotropin.	Obesity
	Orchiectomy Risk-reducing salpingo-oophorectomy	Hypogonadism Hypogonadism	CTIMetS CTIMetS
Radiotherapy	Cranial radiotherapy	Hormonal disturbance: deficiency of growth hormone by damage to the hypothalamus-pituitary axis	Obesity, dyslipidaemia, insulin resistance
	Radiation thyroid gland region	Hypothyroidism: lower basal metabolism	Obesity
	Total body, chest or abdomen	Multiple mechanisms with damage to one or more organs	Hypertension, dyslipidaemia, insulin resistance
Chemotherapy	Cisplatin	Possibly damage to vascular endothelium, possibly through damage to mitochondria and production of ROS	CTIMetS, in particular obesity and dyslipidaemia
	Alkylators, anthracyclines, camptothecins, epipodophyllotoxins	Possibly through damage to mitochondria and production of ROS	Insulin resistance
	Antimetabolites In breast cancer patients	Impaired lipid transport Sarcopenic obesity	Insulin resistance CTIMetS, in particular weight gain
			CTIMetS, in particular dyslipidaemia and insulin resistance
Hormonal therapy	Androgen-deprivation therapy	Hypogonadism	Cardiovascular risk increase, dyslipidaemia
	Anti-estrogenic therapy	Hormonal disturbance, possibly by inhibition of aromatase and less production of NO with less protective effect on ischemia	
Other	Muscle atrophy and inactivity	Decreased insulin-stimulated glucose uptake	Insulin resistance, obesity
	Dietary restriction and antibiotics	Disruption and damage to the intestinal flora with reduced dietary uptake and insulin secretion	Insulin resistance

obesity, dyslipidaemia and insulin resistance (Janiszewski et al., 2007). Growth hormone contributes to lipolysis and has an insulin-like influence. For example, it stimulates production of insulin-like growth factor-1, with glucose uptake as a result (de Haas et al., 2010).

Hypothyroidism is seen in patients after radiation to the thyroid gland region (e.g. patients with head and neck cancer or Hodgkin's disease). Bölling et al. reported that 24% of patients (median follow-up of 40 months) who received radiotherapy to the thyroid gland and/or pituitary showed elevated subclinical thyroid-stimulating hormone (TSH) values (Bölling et al., 2011). In only

37% of these patients, TSH values normalized without intervention during follow-up. Hypothyroidism, and even low-normal thyroid hormone levels, can cause a lower basal metabolism and induce weight gain, which can lead to CTIMetS (Roos et al., 2007).

In a large cohort of 8599 childhood cancer survivors (52% male) and 2936 siblings (46% male), 5096 patients (59.3%) were treated with cranial, abdominal, chest, total body, combination or other radiotherapy. Meacham et al. (2010) showed that exposure to radiotherapy was associated with three or more of the following outcomes: body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, use of medication for hypertension, dyslipidaemia and impaired glucose metabolism

**Table 3**

Increased risk of cancer treatment-induced metabolic syndrome described in several studies in different patient groups with odds ratios or relative risk compared to controls.

Patient group	Author, journal and year of publication	Number of patients	Control group	Metabolic syndrome OR or RR	95% CI	Follow-up time in years	Treatment type with most impact
Breast cancer survivors (postmenopausal)	Buttros Dde et al. (2013) <i>Menopause</i>	104	208 postmenopausal women	OR 1.66	1.04–2.68	Mean 9.4 (SD 4.4) years after diagnosis	NS
Prostate cancer patients treated with ADT	Braga-Basaria et al. (2006) <i>J Clin Oncol</i>	20	18 non-ADT and 20 healthy, all age-matched	OR 4.58	1.41–14.86	Still under treatment	Androgen deprivation (hormonal) therapy
Survivors of childhood cancer	Meacham et al. (2010) <i>Cancer Epidemiol Biomarkers Prev</i>	8599	2936 siblings	OR 1.3 <sup>a</sup>	0.9–1.9	5 years or more after diagnosis, not further specified	Radiotherapy, especially total body irradiation and to the chest
Survivors of childhood acute myeloid leukaemia	Blijdorp et al. (2013) <i>Leukemia research</i>	12 CT and 9 SCT <sup>b</sup>	60 siblings, friends or neighbours with same sex and age range of 5 yr related to survivor	OR 1.31 and OR 24.1	NS	Median 21.6 (Range 9.1–30.7) and 19.0 (Range 11.6–30.0)	Stem cell transplantation
Survivors of haematologic malignancies	Li et al. (2015) <i>Med Oncol</i> <sup>c</sup>	191	2406 healthy controls	OR 2.37	1.70–3.31	NS	Hematologic stem cell transplantation
Survivors of acute lymphoblastic leukaemia	Nottage et al. (2014) <i>Br J Haematol</i>	784	777 age, sex and race-matched controls	RR 1.43	1.22–1.69	26.1 (11–45.3)	Cranial radiotherapy
Hereditary breast and/or ovarian cancer patient	Michelsen et al. (2009) <i>Eur J Cancer</i>	326	679 age adjusted, general population with no removal of uterus/ovaries	OR 2.46	1.63–3.73	Mean 6.5 (SD 4.4) after surgery	Surgery
Testicular cancer survivors	Willemse et al. (2013) <i>Br J Cancer</i>	251	360 healthy, age-adjusted	OR 1.9	1.1–3.2	Mean 7.8 (SD 7.4) after treatment	Combination chemotherapy
	Haugnes et al. (2007) <i>Ann Oncol</i>	1135	1150 healthy controls <60 year, without testosterone supplementation	OR 2.1 <sup>d</sup>	1.3–3.4	Median 9.4 (Range 5–20) <sup>e</sup>	Combination chemotherapy with cumulative cisplatin dose > 850 mg

For this table, articles published in English were selected with the search terms [metabolic syndrome x] AND [survivors] AND [neoplasms (or specific, for example 'breast neoplasms')]. For prostate cancer, [survivors] was not used, because this patient group mainly involves patients who are still under treatment. Other selection criteria were: a clear odds ratio or relative risk was given or could be extracted from the data, a control group was used, no intervention was observed and the MetS was defined according to the NCEP ATP III criteria.

OR: odds ratio; CI: confidence interval; SD: standard deviation; NS: not specified; ADT: androgen deprivation therapy; CT: chemotherapy; SCT: Stem cell transplantation; RR: relative risk.

<sup>a</sup> A surrogate endpoint for MetS was used: Cardiovascular Risk Factor Cluster.

<sup>b</sup> 12 patients treated with chemotherapy and 9 with treated with stem cell transplantation.

<sup>c</sup> In a meta-analysis of 7 studies, 3 studies used NCEP ATPIII criteria. The combined numbers and OR of these 3 studies was given, calculated by Li et al.

<sup>d</sup> OR which was calculated in patients with a cumulative cisplatin dose of >850 mg compared to controls.

<sup>e</sup> the follow-up time of the group cisplatin >850 mg was used.

(Table 3). In the complete cohort, childhood cancer survivors were more likely than siblings to take medications for hypertension (OR 1.9, 95% CI 1.6–2.2), dyslipidaemia (OR 1.6, 95% CI 1.3–2.0) or diabetes (OR 1.7, 95% CI 1.2–2.3). A combination of direct vascular toxicity, damage to multiple endocrine organs, like the hypothalamus, the pituitary, the thyroid gland or the gonads is probably responsible (Meacham et al., 2010).

### 3.3. The role of chemotherapy

Chemotherapy appears to contribute to the pathophysiology of CTIMetS partially through gonadal toxicity. Chemotherapy may induce decreased levels of estrogens and testosterone, which are associated with central obesity, dyslipidaemia and insulin resistance (Carr, 2003; Laaksonen et al., 2004). Alkylating agents, such as cyclophosphamide and heavy metals, like platinum, are known to induce gonadal function impairment (de Haas et al., 2010). In testicular cancer survivors, treatment with chemotherapy is associated with an increased risk of developing CTIMetS. Weight gain in testicular cancer survivors is most common in patients who have received chemotherapy. Patients who were treated with cisplatin > 850 mg had a significantly higher mean 10-year BMI change compared to patients who were treated with surgery only. Patients

treated with radiotherapy or lower dose cisplatin ( $\leq 850$  mg) had no significant 10-year BMI change compared to surgery. This suggests that chemotherapeutic treatment with high dosage of cisplatin is related to weight gain (Table 3) (Sagstuen et al., 2005). In a study in 173 testicular cancer survivors versus 1085 controls from the background population with a median follow-up of 5 years, de Haas et al. (2013) reported that CTIMetS developed at a younger age in testicular cancer survivors treated with chemotherapy. It was also found that at a median follow-up of 5 years (range 3–20) and attained age of 37 years (range 19–59), 44% of the patients had a low high density lipoprotein cholesterol ('good' cholesterol) (HDL-C) with an OR of 1.7 (95% CI 1.2–2.3) and 29% had high triglycerides with an OR of 1.2 (95% CI 0.8–1.7) in comparison to healthy age-adjusted controls. In this study, patients with low testosterone levels (<15 nmol/l) appeared to have an increased risk of CTIMetS (OR 4.1, 95% CI 1.8–9.3) (de Haas et al., 2013).

The postmenopausal transition in healthy women comes with declines in lean body mass and increases in fat mass due to natural ageing, especially in the first postmenopausal years (Wang et al., 1994). Menopause may develop earlier than expected in cancer survivors due to chemotherapeutic treatment. It can be difficult to determine whether changes in adipose tissue and lean mass in these women represent a natural process or an accel-



erated and deleterious process induced by the cancer treatment, called sarcopenic obesity (Rock and Demark-Wahnefried, 2002). Nevertheless, it is clear that many women treated for breast cancer gain weight, sometimes with serious consequences like CTIMetS and cardiovascular disease (American society of clinical oncology obesity and cancer toolkit, 2014). In the systematic review of Vance et al., women who had received chemotherapeutic treatment were most at risk for gaining weight. Weight gains of 2.5–6.2 kg were most commonly reported (Vance et al., 2011). Irwin et al. also observed greater weight gain in postmenopausal breast cancer patients receiving chemotherapy compared to patients receiving surgery or surgery plus radiotherapy (Irwin et al., 2005). This was also observed by Goodwin et al. (1999) who reported that onset of menopause and chemotherapy independently predict weight gain. However, it is still unclear whether breast cancer survivors gain more weight over time compared to the background population, also taking into account the potential development of early menopause and increased obesity in the general population.

Insulin resistance, hyperinsulinaemia or elevated glucose levels are important aspects of MetS and can also be induced by chemotherapeutic cancer treatment. A direct influence of various chemotherapeutic agents on insulin sensitivity is thought to be responsible for this. For alkylators, anthracyclines, camptothecins (e.g. irinotecan), epipodophyllotoxins (e.g. etoposide) and platinum-based treatments this could be due to mitochondrial dysfunction through increased production of reactive oxygen species (ROS) (Rosen et al., 2013). Antimetabolites such as capecitabine can decrease hepatic lipid export, causing steatosis, which is associated with decreased insulin sensitivity (Floyd et al., 2006). In addition, a concomitant cytotoxic treatment adverse event like anaemia may cause adipose tissue hypoxia, leading to macrophage activation and inflammatory cytokine release (Rosen et al., 2013). These examples show that chemotherapy contributes to the development of CTIMetS mostly through weight gain, but may also indirectly affect other MetS components like dyslipidaemia or insulin resistance.

### 3.4. The role of hormonal therapy

The hormone-modifying treatment with androgen-deprivation therapy (ADT) in prostate cancer survivors is associated with components of MetS. Several studies have revealed that drug-induced hypogonadism causes dyslipidaemia in prostate cancer patients (Saylor and Smith, 2009; Shahani et al., 2008). Shahani et al. reported a few studies which all showed elevation of triglycerides and low density lipoprotein cholesterol (LDL-C). However, HDL-C also increased in some studies, which makes it difficult to quantify the cardiovascular risk in this group of patients (Shahani et al., 2008). Keating et al. described an adjusted hazard ratio of 1.44 in incident diabetes in men who were treated with a gonadotropin-releasing hormone agonist (Keating et al., 2006). Furthermore, in patients with pre-existing diabetes, glycaemic control worsened: 19.5% had an increase of HbA1c  $\geq 10\%$  and 28.6% had an increase of fasting blood glucose levels  $\geq 10\%$  (Derweesh et al., 2007). In low-risk prostate cancer, the risk of cardiovascular disease may outweigh the potential benefit of ADT, negatively influencing overall survival in these patients (Saigal et al., 2007).

Anti-estrogenic therapy is commonly used to treat estrogen-receptor positive breast cancer. Because MetS can be a risk factor for the development of cardiovascular disease, the effects of aromatase inhibitors and tamoxifen on lipid levels and other cardiovascular risk factors, are noteworthy. Regarding cardiac adverse events, aromatase inhibitors appear to have a slightly more unfavourable profile than tamoxifen (absolute difference of 0.52%; RR 1.31, 95% CI 1.07–1.60;  $P=0.007$ ), but tamoxifen may increase the risk of thrombo-embolism (RR 0.53 95% CI 0.42–0.65,  $P<0.0001$  in favour of aromatase inhibitors) (Cuppone et al., 2008). Concerning lipid

profile, tamoxifen appears to significantly decrease total cholesterol and LDL-C levels in comparison to the aromatase inhibiting drugs anastrozole and exemestane. Triglycerides tend to increase slightly with tamoxifen, and HDL-C only differs between the two aromatase inhibiting drugs (Hozumi et al., 2011). Animal studies have shown that aromatase is highly present in the cardiovascular system, especially in the endothelial and smooth muscle system, which could explain the apparently unfavourable cardiovascular effect of aromatase inhibiting drugs. Aromatase inhibition leads to inhibition of estrogen synthesis, resulting in lower nitric oxide production, which impairs the protective effect of nitric oxide against ischemia (Jazbutyte et al., 2012).

### 3.5. Other cancer treatment-induced mechanisms

Physical inactivity and poor health often coexist during cancer treatment and may also be responsible for atrophy and less muscle tissue, which in turn induces a decrease in insulin-stimulated glucose uptake (Rosen et al., 2013). Damage to the gastrointestinal tract and liver may also impair insulin sensitivity. Gut motility is impaired not only by drugs such as vinca alkaloids, but also by disruption of the intestinal flora by dietary restrictions and antibiotics, which are also commonly used during chemotherapy. This results in a reduction of dietary uptake and influences the balance of motility and insulin secretion (Samuel et al., 2008; Stringer et al., 2009). Notably, inactivity, obesity and diabetes are also risk factors for the development of various types of cancer. Therefore, at baseline, cancer patients may already have a higher chance of developing or having the MetS (Mendonça Fernando Miguel, 2015).

## 4. Intervention options for the metabolic syndrome

### 4.1. Non-cancer population

In the non-cancer population, achieving a healthy lifestyle by increasing physical activity in combination with dietary measures and smoking cessation has been shown to improve the individual components of MetS and should be the first step in treatment (Grundy et al., 2005). The mainstay in the treatment of MetS is achieving an optimized energy balance, i.e. a proper balance between caloric intake and expenditure. More and more data are available on beneficial effects of lifestyle interventions to treat MetS and to prevent cardiovascular disease. Yamaoka and Tango (2012) included eight randomized clinical trials with combined diet and exercise or dietary education alone interventions in their meta-analysis and concluded that a lifestyle modification intervention resolved MetS approximately 2.0 times more often compared with the control group (95% CI 1.5–2.7). These lifestyle interventions led to significant reductions in systolic blood pressure, triglyceride levels, waist circumference and fasting blood glucose levels. Edwardson et al. (2012) showed that more time spent in sedentary behaviour increased the odds of MetS by 73% (OR 1.73, 95% CI 1.55–1.94;  $P<0.0001$ ). Blüher et al. (2014) studied obese and overweight children, providing them with a one-year lifestyle intervention which contained regular exercise, diet counselling, healthy meal preparation, psychological counselling, education about the medical background of obesity and education of parents. After the intervention they measured significant improvements in anthropometric parameters and body composition as well as metabolic risk markers and glycaemic control. For example, the standard deviation score, a normalized score for comparison between children of different age and sex, for percentage body fat was 1.79 at baseline and decreased by  $-0.14$  (95% CI  $-0.18$ ,  $-0.02$ ;  $P=0.01$ ). HbA1c levels also decreased from  $5.5\pm 0.08\%$  at start of the intervention to  $5.2\pm 0.05\%$  after completion ( $P=0.03$ ).

No significant differences in insulin levels were found, but a significant decrease in FFA ( $0.72 \pm 0.03$  vs.  $0.60 \pm 0.04$ ;  $p=0.03$ ) was observed (Blüher et al., 2014). Dalleck et al. (2013) reported a study of 142 men and 190 women (age 28–88) who participated in a 14-week exercise intervention. All components of MetS, except total cholesterol, improved significantly between baseline and 14 weeks, with an absolute elevated energy expenditure of +226.4 kcal/week in men and +191.3 kcal/week in women (Dalleck et al., 2013). Lee et al. (2014) found that adults who practice leisure-time running have a 30% and 45% lower adjusted risk of all-cause and cardiovascular mortality respectively, even with 5–10 min per day at a speed of approximately 10 km/h. These data support a healthy lifestyle as an important part of tackling the MetS, and although (randomized controlled) trials are lacking, this is also true for CTIMetS. The obesity-driven background of both entities also plead for this.

#### 4.2. Cancer survivor population

Previously, the follow-up of long-term adult and childhood cancer survivors focused on early relapse detection and prolongation of cancer-free survival. Currently, follow-up also consists of counselling patients to maintain a healthy long-term survivorship. Oncologists and physicians involved in survivor care should raise awareness among their patients of the potential effects of cancer treatment like cardiometabolic late effects and weight gain. It is assumed that the same strategies can be applied to treat and prevent MetS in the general population and CTIMetS in cancer survivors. However, it is controversial whether the same risk assessment can be performed in cancer survivors compared to the non-cancer population. Accelerated ageing has been described in testicular cancer survivors, including accelerated atherosclerosis, development of cardiovascular events at younger attained age, and premature hormonal ageing (Sprauten et al., 2014). Therefore, one may argue that 10–15 years should be added to age in order to receive a more accurate assessment of cardiovascular risk in these cancer patients, similar to what is advocated in patients with diabetes mellitus (Booth et al., 2006) and rheumatoid arthritis (Peters et al., 2010). Treatment of MetS and CTIMetS consists of lifestyle interventions with or without drug therapy. Adequate pharmacological treatment against CTIMetS with oral anti-diabetics, statins and angiotensin converting enzyme inhibitors is important (Grundy et al., 2005) to improve the long-term outcome of cancer survivors. Currently, estimating cardiovascular risk and the decision to initiate drug treatment to prevent cardiovascular disease is largely based on age. Furthermore, only 10-year risk is predicted, whereas life time risk assessments for this age group are needed (Berry et al., 2012). Standard guidelines are insufficient in the younger cancer survivor population, although these are the patients that would probably benefit most (Rugbjerg Kathrine, 2014).

Regarding treatment with lifestyle interventions, Bao et al. evaluated exercise in a population-based prospective cohort study in 1696 breast cancer survivors. At baseline, the prevalence of MetS was 55.18%. They found that exercise participation of  $\geq 3.5$  h/week (30 min/day) between 6 and 60 months post-diagnosis was inversely associated with the prevalence of MetS with an adjusted OR of 0.69 (95% CI 0.48–0.98). The most reported type of exercise was walking (45.40%). Exercising  $< 3.5$  h/week did not seem to have effect (OR 0.98; 95% CI 0.69–1.40) (Bao et al., 2013).

These results are in accordance with a small exercise intervention study performed by Thomas et al. Breast cancer survivors were randomized into a 6 months aerobic exercise intervention ( $n=35$ ) or usual care ( $n=30$ ). The prevalence of MetS at baseline was 55.4%. In the intervention group, adhering to the exercise intervention resulted in a significant ( $P=0.009$ ) decrease of the MetS from baseline to 6 months in comparison to non-adherers. The authors designed a standardised Z-score to allow compari-

son of MetS instead of separate components. Z-scores of the MetS in the exercise and the usual care group were  $-0.76 \pm 0.36$  and  $0.80 \pm 0.42$  respectively (Thomas Gwendolyn, 2013). Furthermore, Ligibel et al. showed that fasting insulin concentrations of breast cancer patients who attended a 16-week exercise intervention decreased by an average of 2.86 microU/ml ( $P=0.03$ ) in comparison to a decrease in the usual care group of 0.27 microU/ml ( $P=0.65$ ) (Ligibel et al., 2008). Jones et al. (2014) reported the adjusted rate ratio for cardiovascular events in survivors of childhood Hodgkin lymphoma according to physical activity. They found that the rate of events for patients with zero metabolic equivalent task hours per week (MET hours/week) was 0.87 for 3–6 MET hours/week (95% CI 0.56–1.34), 0.45 for 9–12 MET hours/week (95% CI 0.26–0.80) and 0.47 for 15–21 MET hours/week (95% CI 0.23–0.95). This shows that the protective mechanism of physical activity is to a certain extent dose dependent (Jones et al., 2014).

Besides the fact that cardiorespiratory fitness (CRF) is inversely related to risk of death, cancer incidence (Lakoski et al., 2015) and cancer mortality (Schmid and Leitzmann, 2014), it may also play a role in the development of MetS. Ekblom et al. (2015) found that decreased cardiorespiratory fitness is strongly associated with the prevalence of MetS (OR 0.24, 95%CI 0.12–0.48) and that increased moderate-to-vigorous activity is associated with decreased prevalence of MetS (OR: 0.33, 95% CI 0.18–0.61). In a study with overweight postmenopausal African-American women, Adams-Campbell et al. (2016) found that lower CRF, defined as  $VO_2$  peak  $< 22$  ml/min/kg, was associated with higher prevalence of MetS, abdominal obesity, elevated triglyceride levels and low HDL-C. Lakka et al. (2003) even suggests that poor CRF is a feature of MetS. Probably the association between CRF and MetS also exists in cancer survivors. BMI, body fat percentage and waist circumference are all inversely associated with CRF in breast cancer survivors. This association suggests that when one's BMI, body fat percentage and waist circumference increases, CRF declines (Orozco et al., 2016). This relation was also found in a study with endometrial cancer survivors. At baseline, obese survivors had poorer CRF ( $p=0.002$ ) and also higher systolic blood pressure ( $p=0.018$ ) compared to non-obese survivors.

Although lifestyle interventions are not a routine part of cancer care (Ligibel et al., 2015), these studies support the hypothesis of exercising as a good and easy accessible intervention against CTIMetS. Results on the lasting effect of lifestyle interventions in cancer survivors are still scarce, but the available short-term evidence is promising. In particular, self-efficacy, education and tailored interventions seem to have a long-term effect (Demark-Wahnefried et al., 2007). Nevertheless, it is clear that more and long-term data on this subject are needed (Ligibel et al., 2015).

##### 4.2.1. Timing

Timing of lifestyle intervention is a relevant and interesting issue. Lifestyle interventions are most frequently started after completion of cancer treatment. Mounting evidence on the negative impact of overweight on the outcome of cancer treatment (Ewertz et al., 2011; Jiralerspong et al., 2013) has made the issue of timing lifestyle interventions more urgent. In 2010, the roundtable on exercise guidelines for cancer survivors from the American College of Sports Medicine (ACSM) concluded that exercise training both after and during cancer treatment is safe and results in improvements in physical functioning, quality of life and cancer-related fatigue in several cancer groups (Schmitz et al., 2010; Courneya et al., 2013). Nevertheless, it is still unknown if there is a difference between exercising during or after cancer treatment and to what extent.

For the prevention of CTIMetS and cardiovascular disease that is induced by cancer treatment, earlier initiation of a tailored lifestyle intervention may be appropriate. For example, change of body com-

position and weight gain, the potential driving force of CTIMetS, may be alleviated or prevented if patients start changing lifestyle habits early and during treatment. Resistance training may prevent excessive loss of lean body mass, and aerobic training may increase physical functioning and CRF and prevent increase of body fat mass. Also, bone health can be maintained and bone density loss can be prevented (Winters-Stone et al., 2013). If patients succeed in maintaining a healthy weight and body composition, the development of insulin resistance, hyperinsulinaemia and dyslipidaemia may be prevented. If weight is not maintained, exercise is still an effective way to combat the other components of MetS. Another advantage of initiating an exercise intervention during cancer treatment is that patients become acquainted with this lifestyle change and start incorporating it into their own lives. Patients who are already exercising can struggle with the intensity and frequency of exercise during treatment. A professional intervention can provide support.

Effective lifestyle interventions initiated early during intensive cancer treatment make optimal use of the “teachable moment” (Demark-Wahnefried et al., 2005), when thoughts about consequences of lifestyle and attempts to influence outcome of disease are very common. This contemplation phase appears to be an appropriate moment to encourage patients to change unhealthy behaviour and provide the tools to do that. Education about lifestyle and emphasizing the positive effects of lifestyle change for long-term cancer survivorship is helpful at this time.

## 5. Conclusion

Numbers of cancer survivors are increasing as a result of earlier detection and more effective and intensive treatment strategies. This has resulted in better overall survival but also in more cancer treatment related morbidity, like cancer treatment-induced metabolic syndrome (CTIMetS). CTIMetS differs from non-CTIMetS in aetiology. However, intervention or prevention strategies, i.e. lifestyle interventions, can be similar, because they often share an obesity driven background. But this is not the case in all cancer patients or treatment types. The complexity of MetS is that many factors play a role, including cardiorespiratory fitness. However, when obesity is prevented or treated, the major catalysing component is probably been dealt with. Lifestyle interventions, whether or not provided in a supervised schedule, may play a key role. Lifestyle interventions are a safe and excellent method for prevention or treatment of CTIMetS, probably even during curative systemic treatment. Based on mounting evidence we feel that it is justified to implement lifestyle interventions with the goal to optimize energy balance as a part of standard cancer treatment. The longer this is postponed, the longer we withhold these patients a good opportunity for healthy survivorship. However, we still need longer follow-up and more data about accurate timing of these lifestyle interventions. Ultimately, these interventions should also improve outcome, including late morbidity and overall mortality.

## Contributors

NLW, JN, JAG and AMEW were responsible for the design of the review and collection of data. NLW contributed to the design of the figure with the use and permission of Servier medical art database. All authors wrote and approved the final manuscript.

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## Conflict of interest statement

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